REMARKS/ARGUMENTS

Reconsideration and withdrawal of the rejections of the present application are respectfully requested in view of the amendments to the claims and remarks presented herewith, which place the application into condition for allowance.

Status of the Claims and Formal Matters

After the amendments made herein, claims 1, 7-10, 34, 36-39 and 271 are currently pending in this application. By this paper, Claims 12-19, 40-47, and 272-276 have been cancelled, and Claims 1, 34, and 271 have been amended, without prejudice, and solely to expedite prosecution pursuant to the U.S. Patent and Trademark Office Business Goals (65 Fed. Reg. 54604 (September 8, 2000)). Claims 6, 11, and 35 were previously cancelled, without prejudice or disclaimer. Applicants assert the right to reclaim cancelled subject matter in co-pending applications.

No new matter has been introduced by these amendments. Support for the amended recitations can be found throughout the specification as originally filed, such as, for example, page 11, lines 5-6 and 11-13 of the instant specification as originally filed.

Priority Claim

The Office Action alleges that the instant application should be accorded the filing date of March 4, 2003, the filing date of the parent application (Serial No. 10/379,149) because the priority application (Serial No. 60/361,759) allegedly fails to provide adequate support or enablement for "methods of treating cutaneous T-cell lymphoma in a subject comprising orally administering a total daily dose of 200-600 mg" of the histone deacetylase inhibitor SAHA. By this paper, Applicants have amended the priority claim of the present application, without prejudice and without admission. Therefore, the instant application carries a filing date of July 9, 2003 and does not make any claims of priority.

Rejections under 35 U.S.C. §103(a)

Claims 1, 12-19, 34, 40-47, and 271-276 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Breslow et al. (U.S. Patent No. 6,087,367; hereinafter

"Breslow") in view of Curley et al. (Proceedings of ASCO, 2002, vol. 21, page 6b, entry 1831; "Curley") and Piekarz et al. (Blood, 2001, vol. 98, pages 2865-2868; "Piekarz"). Claims 12-19, 40-47, and 272-276 have been cancelled herein. Applicants traverse with regard to the remaining pending claims. Applicants also submit the Declaration of Dr. Madeleine Duvic under 37 C.F.R. §1.132 ("Duvic Decl. ¶ _").

The claimed invention relates to methods of treating cutaneous T-cell lymphoma (CTCL) by administration of a once-daily continuous dose of about 400 mg of SAHA, or a twice-daily dose of about 300 mg of SAHA administered for 14 out of 21 days. Breslow, Curley, and Piekarz, whether considered alone or in combination with each other, do not teach or suggest all of the instant claim limitations as required to establish *prima facie* obviousness under §103(a), particularly once-daily, continuous administration of 400 mg of SAHA and twice-daily administration of 300 mg of SAHA for 14 out of 21 days, for treatment of cutaneous T-cell lymphoma.

According to the Office Action, Breslow allegedly teaches methods of selectively inducing terminal differentiation of neoplastic cells and thereby inhibiting proliferation of such cells by administration of a histone deacetylase inhibitor compound. The Examiner concedes that Breslow does not expressly disclose the instantly claimed oral doses and dosage regimens of SAHA or the specific treatment of cutaneous T-cell lymphoma ("CTCL") with SAHA. Applicants agree that Breslow does not teach or suggest oral administration of SAHA to treat cutaneous T-cell lymphoma at the claimed dosage ranges and dosing schedules. So does Dr. Duvic. Duvic Decl. ¶ 6. Breslow is fatally deficient.

Curley does not remedy the deficiencies of Breslow, as described in Duvic Decl. ¶ 7. Curley describes a clinical study that tested orally administered doses of SAHA ranging from 200 mg daily, 400 mg daily, 400 mg twice a day, 800 mg twice a day, 1600 mg twice a day, to 2000 mg twice a day. As provided by Dr. Duvic, Curley is deficient because there is no teaching, suggestion, or disclosure of oral continuous once-daily administration of 400 mg of SAHA (as recited in Claim 1 and the claims depending therefrom), or oral twice-daily administration of 300 mg of SAHA administered for 14 days out of each 21 days (as recited in Claim 34 and the claims

that depend therefrom) to treat CTCL. These specific treatment regimens are unexpectedly superior in the treatment of CTCL, as Dr. Duvic reported in a peer-reviewed publication that reports the results of a Phase II clinical trial of oral SAHA for the treatment of CTCL.

Piekarz is also fatally lacking and does not cure the deficiencies of Breslow and Curley. The Examiner notes that Piekarz refers to use of depsipeptide in the treatment of CTCL. However, Piekarz does not refer to use of SAHA in the treatment of CTCL. Rather Piekarz refers to a structurally distinct molecule -- depsipeptide is a cyclic peptide molecule, while SAHA is a hydroxamic acid compound. Furthermore, the two drugs do not share the same mechanism of action, for example, in view of sensitivity of depsipeptide to P-glycoprotein (Pgp). Notably, depsipeptide cannot kill cells expressing Pgp, while SAHA is unaffected by the presence of Pgp in cells. In addition, SAHA can reversibly bind and inhibit class I (HDACs 1, 2, 3, and 8) and class II (HDACs 4, 5, 7, and 9) histone deacetylases, whereas depsipeptide preferentially inhibits class I HDACs over class II HDACs, especially HDAC1 and 2 (see, for example, Bolden et al., (2006) Nat. Rev. Drug Discov. 5(9): 769-84). SAHA and depsipeptide also each elicit subtle, yet significant differences in the mechanism of action in intrinsic apoptotic pathways. For example, SAHA is not unaffected by the pan-caspase inhibitor ZVAD-fmk, while depsipeptide-induced cleavage of the apoptosis protein Bid is perturbed by ZVAD-fmk, suggesting that depsipeptide-mediated apoptosis requires caspases, but SAHA-mediated apoptosis may not. See Peart et al., (2003) Cancer Res. 63(15): 4460-4471. Moreover, SAHA and depsipeptide induce changes in gene expression of an overlapping, but not identical, set of genes (see, for example, Peart et al., (2005) Proc. Natl. Acad. Sci. 102(10): 3697-702), suggesting that the two drugs may have different mechanisms of action.

Piekarz describes a phase I study of intravenously administered depsipeptide in patients suffering from peripheral and cutaneous T-cell lymphoma. Notably, Piekarz is silent regarding oral administration of SAHA at the instantly claimed doses and dosing schedules and thus fails to cure the defects of Breslow and Curley. As Dr. Duvic states in the Duvic Decl. ¶ 8-10 the suggestion in Piekarz that depsipeptide may be useful in the treatment of CTCL has no bearing on whether a completely unrelated molecule SAHA, is useful in treatment of CTCL (as

claimed). In fact, Piekarz lacks any teaching or disclosure regarding oral administration of SAHA at the instantly claimed doses and dosing schedules and thus fails to cure the defects of Breslow and Curley. Finally, Piekarz administers depsipeptide intravenously. This is a distinct disadvantage in CTCL patients (as discussed in Duvic Decl. ¶ 11). According to the claimed invention, SAHA elicits desirable anti-cancer effects in CTCL patients *via* oral administration.

As Dr. Duvic declaration makes clear at ¶ 10, there are secondary considerations present here that support patentability. In particular, the Duvic study states (page 37, left column, second paragraph) that "[b]ecause the half-life of vorinostat is short (≤ 2 hours), the discontinous dosing schedule of 3 days on and 4 days off used in group 2 may have tipped the balance toward progression compared with continuous therapy regimens of 400 mg daily (group 1) or high dose (300 mg daily for 2 weeks) followed by continuous therapy at 200 mg twice daily (group 3)", indicating that it was surprising and unexpected that continuous administration of 400 mg, or 300 mg daily for 14 out of 21 days would produce a favorable anti-cancer effect in CTCL patients. Therefore, such favorable results from the instantly claimed dosages and dosing schedules from the prior art or the knowledge generally available to those skilled in the art, and that the surprising and unexpected results could only have been obtained by empirically performing the study in patients suffering from CTCL. Duvic Decl. ¶ 11.

For at least all of these reasons, Applicants respectfully request reconsideration and withdrawal of the §103(a) rejection over Breslow, Curley, and Piekarz.

Dependent claims 7-10 and 36-39 (which recite certain excipients) stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Breslow et al. (U.S. Patent No. 6,087,367; hereinafter "Breslow") in view of Curley et al. (Proceedings of ASCO, 2002, vol. 21, page 6b, entry 1831; "Curley") and Piekarz et al. (Blood, 2001, vol. 98, pages 2865-2868; "Piekarz"), as discussed above, further in view of Grant et al. (Pub. No. 2005/0004007; "Grant") and Kabadi (EP 0 547 000 A1; "Kabadi"). Claims 7-10 depend from independent claim 1, and claims 36-39 properly depend from independent claim 34. As discussed above, the combination of Breslow, Curley, and Piekarz does not render claims 1 and 34 obvious. The addition of Grant and Kabadi (cited for reference to those excipients in otherwise unrelated formulations with

unrelated active ingredients) does nothing to cure this deficiency with respect to the dependent claims.

Therefore, Applicants respectfully request withdrawal of the §103(a) rejection over Breslow, Curley, Piekarz, Grant and Kabadi.

CONCLUSION

Favorable action on the merits is respectfully requested. If any discussion regarding this Amendment is desired, the Examiner is respectfully urged to contact the undersigned at the number given below, and is assured of full cooperation in progressing the application to allowance.

Applicants believe no additional fees are due with the filing of this Response. However, if any additional fees are required or if any funds are due, the USPTO is authorized to charge or credit Deposit Account Number: **50-0311**, Customer Number: **35437**, Reference Number: **24852-501 CIP2**.

Respectfully submitted,

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